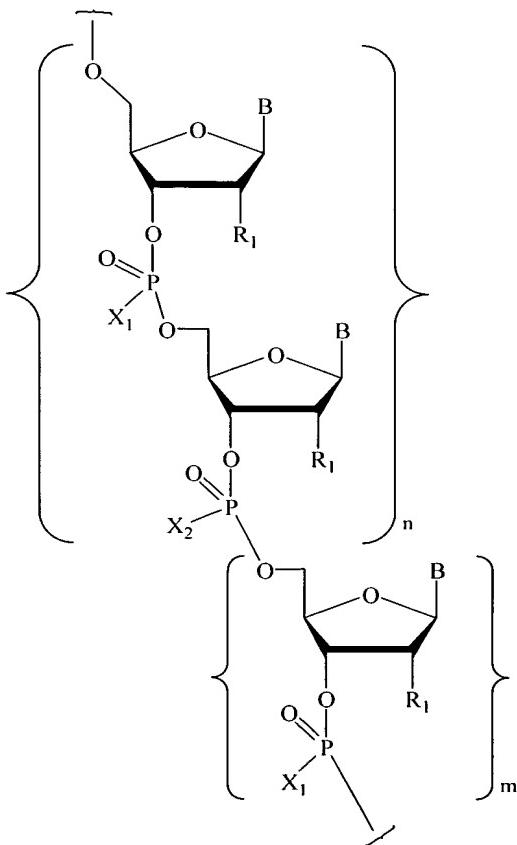


This listing of claims will replace all prior versions, and listings, of claims in the application.

**Listing of Claims:**

1-27. (Canceled).

28. (Previously Presented) A method for reducing the undesired production of a protein in an organism, said method comprising contacting said organism with a compound of formula:



wherein:

each B is a nucleobase;

one of X<sub>1</sub> or X<sub>2</sub> is O, and the other of X<sub>1</sub> or X<sub>2</sub> is S;

each R<sub>1</sub> is, independently, H, hydroxyl, C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>3</sub>-C<sub>20</sub> alkenyl, C<sub>2</sub>-C<sub>20</sub> alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato,

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**Office Action Dated:** January 24, 2005

**PATENT**

sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or  $R_1$  is a group of formula  $Z-R_{22}-(R_{23})_v$ ;

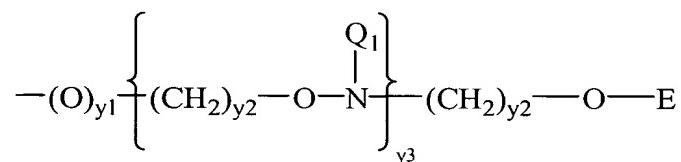
$Z$  is O, S, NH, or  $N-R_{22}-(R_{23})_v$ ;

$R_{22}$  is  $C_1-C_{20}$  alkyl,  $C_2-C_{20}$  alkenyl, or  $C_2-C_{20}$  alkynyl;

$R_{23}$  is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

$v$  is from 0 to about 10;

or  $R_1$  has the formula:



wherein:

$y_1$  is 0 or 1;

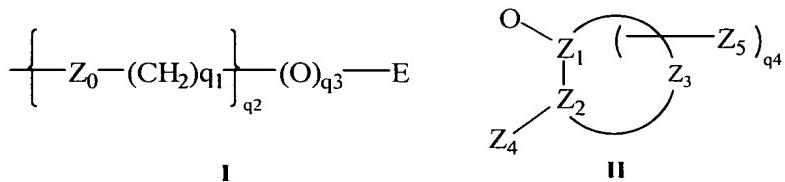
$y_2$  is independently 0 to 10;

$y_3$  is 1 to 10;

$E$  is  $C_1-C_{10}$  alkyl,  $N(Q_1)(Q_2)$  or  $N=C(Q_1)(Q_2)$ ;

each  $Q_1$  and  $Q_2$  is, independently, H,  $C_1-C_{10}$  alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or  $Q_1$  and  $Q_2$ , together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or  $R_1$  has one of formula I or II:



wherein:

$Z_0$  is O, S, or NH;

$q^1$  is from 0 to 10;

$q^2$  is from 1 to 10;

$q^3$  is 0 or 1;

$q^4$  is 0, 1 or 2;

$Z_4$  is  $OM_1$ ,  $SM_1$ , or  $N(M_1)_2$ ;

each  $M_1$  is, independently, H, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> haloalkyl, C(=NH)N(H)M<sub>2</sub>, C(=O)N(H)M<sub>2</sub> or OC(=O)N(H)M<sub>2</sub>;

$M_2$  is H or C<sub>1</sub>-C<sub>8</sub> alkyl;

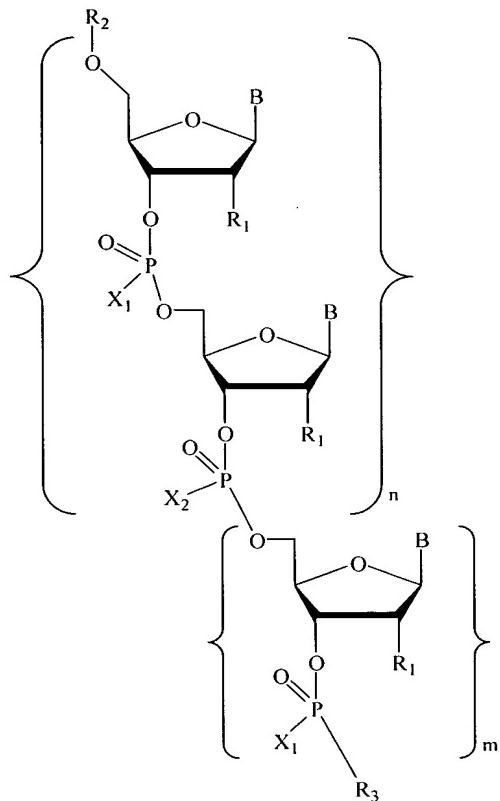
$Z_1$ ,  $Z_2$  and  $Z_3$  comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

$Z_5$  is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, N(Q<sub>1</sub>)(Q<sub>2</sub>), OQ<sub>1</sub>, halo, SQ<sub>1</sub> or CN;

$n$  is from 2 to 50; and

$m$  is 0 or 1.

29. (Previously Presented) A method for reducing the undesired production of a protein in an organism, said method comprising contacting said organism with a compound of formula:



wherein:

each B is a nucleobase;

X<sub>1</sub> is S;

X<sub>2</sub> is O;

each R<sub>1</sub> is, independently, H, hydroxyl, C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>3</sub>-C<sub>20</sub> alkenyl, C<sub>2</sub>-C<sub>20</sub> alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or R<sub>1</sub> is a group of formula Z-R<sub>22</sub>-(R<sub>23</sub>)<sub>v</sub>;

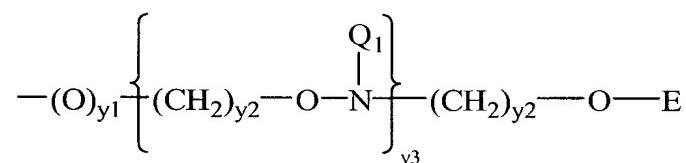
Z is O, S, NH, or N-R<sub>22</sub>-(R<sub>23</sub>)<sub>v</sub>;

R<sub>22</sub> is C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>2</sub>-C<sub>20</sub> alkenyl, or C<sub>2</sub>-C<sub>20</sub> alkynyl;

$R_{23}$  is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

$v$  is from 0 to about 10;

or  $R_1$  has the formula:



$y1$  is 0 or 1;

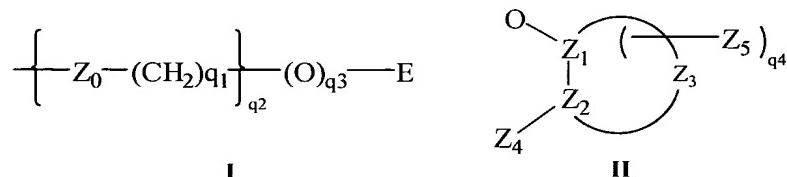
$y2$  is independently 0 to 10;

$y3$  is 1 to 10;

$E$  is  $C_1-C_{10}$  alkyl,  $N(Q_1)(Q_2)$  or  $N=C(Q_1)(Q_2)$ ;

each  $Q_1$  and  $Q_2$  is, independently, H,  $C_1-C_{10}$  alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or  $Q_1$  and  $Q_2$ , together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or  $R_1$  has one of formula I or II:



wherein:

$Z_0$  is O, S, or NH;

$q^1$  is from 0 to 10;

$q^2$  is from 1 to 10;

$q^3$  is 0 or 1;

$q^4$  is, 0, 1 or 2;

$Z_4$  is  $OM_1$ ,  $SM_1$ , or  $N(M_1)_2$ ;

each  $M_1$  is, independently, H, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> haloalkyl, C(=NH)N(H)M<sub>2</sub>, C(=O)N(H)M<sub>2</sub> or OC(=O)N(H)M<sub>2</sub>;

$M_2$  is H or C<sub>1</sub>-C<sub>8</sub> alkyl;

$Z_1$ ,  $Z_2$  and  $Z_3$  comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

$Z_5$  is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, N(Q<sub>1</sub>)(Q<sub>2</sub>), OQ<sub>1</sub>, halo, SQ<sub>1</sub> or CN;

n is from 2 to 50; and

m is 0 or 1;

R<sub>2</sub> is H, a hydroxyl protecting group, or an oligonucleotide; and

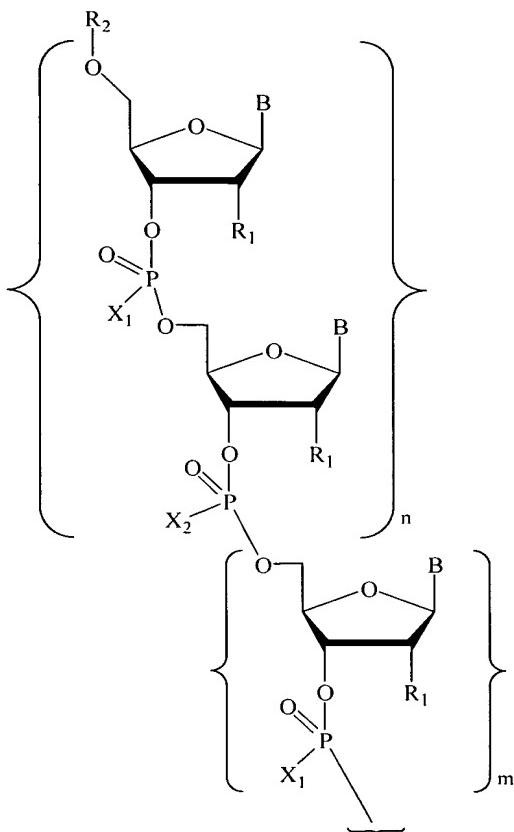
R<sub>3</sub> is OH, an oligonucleotide, or a linker connected to a solid support.

30. (Previously Presented) A method for reducing the undesired production of a protein in an organism, said method comprising contacting said organism with a compound of formula:

(5') W<sup>1</sup>-W<sup>2</sup>-W<sup>3</sup> (3')

wherein:

W<sup>1</sup> has the Formula:



wherein:

each B is a nucleobase;

one of  $X_1$  or  $X_2$  is O, and the other of  $X_1$  or  $X_2$  is S;

each  $R_1$ , is, independently, H, hydroxyl,  $C_1$ - $C_{20}$  alkyl,  $C_3$ - $C_{20}$  alkenyl,  $C_2$ - $C_{20}$  alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or  $R_1$  is a group of formula  $Z-R_{22}-(R_{23})_v$ ;

$Z$  is O, S, NH, or  $N-R_{22}-(R_{23})_v$ ;

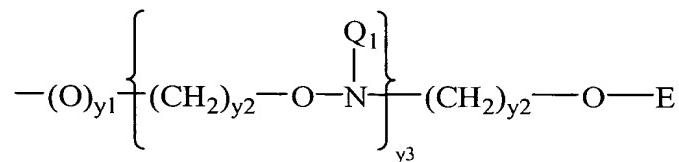
$R_{22}$  is  $C_1$ - $C_{20}$  alkyl,  $C_2$ - $C_{20}$  alkenyl, or  $C_2$ - $C_{20}$  alkynyl;

$R_{23}$  is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-

aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

v is from 0 to about 10;

or R<sub>1</sub> has the formula:



y1 is 0 or 1;

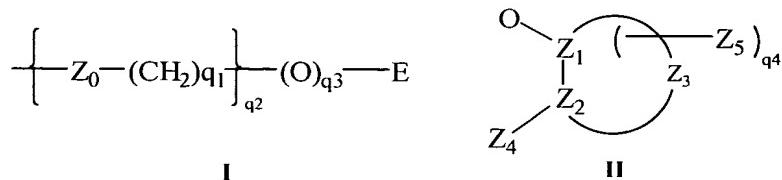
y2 is independently 0 to 10;

y3 is 1 to 10;

E is C<sub>1</sub>-C<sub>10</sub> alkyl, N(Q<sub>1</sub>)(Q<sub>2</sub>) or N=C(Q<sub>1</sub>)(Q<sub>2</sub>);

each Q<sub>1</sub> and Q<sub>2</sub> is, independently, H, C<sub>1</sub>-C<sub>10</sub> alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or Q<sub>1</sub> and Q<sub>2</sub>, together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or R<sub>1</sub> has one of formula I or II:



wherein:

Z<sub>0</sub> is O, S, or NH;

q<sup>1</sup> is from 0 to 10;

q<sup>2</sup> is from 1 to 10;

q<sup>3</sup> is 0 or 1;

q<sup>4</sup> is, 0, 1 or 2;

$Z_4$  is  $OM_1$ ,  $SM_1$ , or  $N(M_1)_2$ ;  
each  $M_1$  is, independently, H, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> haloalkyl, C(=NH)N(H)M<sub>2</sub>,  
 $C(=O)N(H)M_2$  or  $OC(=O)N(H)M_2$ ;

$M_2$  is H or C<sub>1</sub>-C<sub>8</sub> alkyl;

$Z_1$ ,  $Z_2$  and  $Z_3$  comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

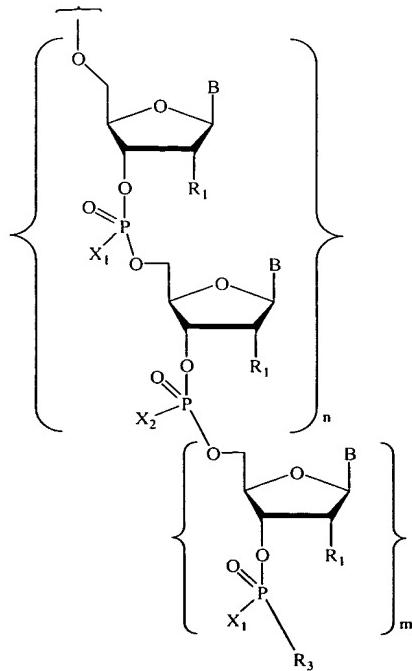
$Z_5$  is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms,  $N(Q_1)(Q_2)$ ,  $OQ_1$ , halo,  $SQ_1$  or  $CN$ ;

$n$  is from 2 to 50; and

$m$  is 0 or 1;

$R_2$  is H, a hydroxyl protecting group, or an oligonucleotide;

$W^3$  has the Formula:



wherein  $R_3$  is OH, an oligonucleotide, or a linker connected to a solid support; and

$W^2$  is a plurality of covalently bound nucleosides linked by phosphodiester or phosphorothioate linkages.

31-51. (Canceled).

52. (Previously presented) The method of claim 28 wherein R<sub>1</sub> is -O-CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>3</sub>.

53. (Previously presented) The method of claim 28 wherein n is about 5 to about 50.

54. (Previously presented) The method of claim 28 wherein n is about 8 to about 30.

55. (Previously presented) The method of claim 28 wherein n is about 4 to about 15.

56. (Previously presented) The method of claim 28 wherein n is 2 to about 10.

57. (Previously presented) The method of claim 29 wherein R<sub>1</sub> is -O-CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>3</sub>.

58. (Previously presented) The method of claim 29 wherein R<sub>2</sub> is H, and R<sub>3</sub> is OH.

59. (Previously presented) The method of claim 29 wherein R<sub>2</sub> is a phosphodiester-linked oligonucleotide or a phosphorothioate linked oligonucleotide.

60. (Previously presented) The method of claim 29 wherein R<sub>3</sub> is a phosphodiester-linked oligonucleotide or a phosphorothioate linked oligonucleotide.

61. (Currently Amended) The method of claim 29 wherein R<sub>2</sub> and R<sub>3</sub> are each a phosphodiester-linked oligonucleotide or a phosphorothioate linked oligonucleotide.

62. (Previously presented) The method of claim 30 wherein R<sub>1</sub> is -O-CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>3</sub>.

63. (Previously presented) The method of claim 30 wherein R<sub>2</sub> is H, and R<sub>3</sub> is OH.
64. (Previously presented) The method of claim 30 wherein n is about 5 to about 50.
65. (Previously presented) The method of claim 30 wherein n is about 8 to about 30.
66. (Previously presented) The method of claim 30 wherein n is about 4 to about 15.
67. (Previously presented) The method of claim 30 wherein n is 2 to about 10.
68. (Previously presented) The method of claim 30 wherein W<sup>2</sup> is a plurality of covalently bound nucleosides linked by phosphodiester linkages.
69. (Previously presented) The method of claim 30 wherein W<sup>2</sup> is a plurality of covalently bound nucleosides linked by phosphorothioate linkages.